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Intramolecular Diels–Alder reaction for the synthesis of tetracyclic carbazoles and isocanthines

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ABSTRACT

One pot intramolecular Diels–Alder reaction has been efficiently used as a new route for the synthesis of four tetracyclic carbazoles and four isocanthine analogues where a dialdehyde is utilised as a common intermediate for both the scaffolds. Biological activity was evaluated for some molecules, which demonstrated moderate activity against HeLa cervical cancer cell lines.

1. Introduction

Tetracyclic carbazole analogue **X** (Fig. 1) has carbazole as a basic skeleton, which is a common artifact of many natural products having biological activity, such as inhibitory activity against cyclin-dependent kinase 4 and antiproliferative activity in a human colon carcinoma cell line,[1] antiplatelet aggregation activity,[2] inhibition against pRb phosphorylation[3] etc. Several routes are available for the synthesis of derivatives of tetracyclic carbazole **X**, which involve mainly photocyclisation,[4] Heck coupling[5] and Diels–Alder reactions as key steps.[6]

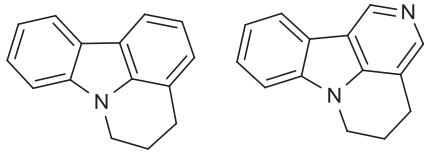

Fig. 1. Tetracyclic carbazole and isocanthine skeleton.

Isocanthines are heterocyclic analogues of carbazoles, which are γ-carboline alkaloids possessing a tetracyclic skeleton **Y** as shown in Fig 1. These alkaloids are known to act as cardiovascular agent[7] and $5HT_3$ receptor antagonist.[8] Palladium-catalysed intramolecular annulation[9] and hetero Diels–Alder reaction[10] have been used for the synthesis of isocanthines in the past. Recently, a one pot electrocyclisation strategy and intramolecular aza-Diels–Alder (ADA) reaction approach have been developed in our group for the synthesis of γ-carboline derivatives[11] and for new canthine analogues,[12] respectively.

In continuation with this, the present work describes the use of intramolecular Diels–Alder strategy for an efficient and short synthesis of substituted tetracyclic carbazole and isocanthine analogues using dialdehyde as a common intermediate.

2. Results and discussion

The synthesis was planned as shown in the retrosynthetic analysis (Scheme 1) where in, dialdehyde would be a common intermediate to achieve both the target scaffolds.

The scheme towards tetracyclic carbazole started with formylation of indole **1**, using Vilsmeier–Haack conditions (Scheme 2). 3-Formyl indole **2** was then treated with 4-chloro-butan-1-ol, to get the *N*-alkylated 3-formyl indole **3**. Compound **3** was oxidised using *o*-iodoxybenzoic acid (IBX) to deliver the intermediate dialdehyde **4**. Refluxing dialdehyde **4** in toluene with excess of carbethoxymethylenetriphenyl phosphorane (4 equiv), for 8 h, afforded *trans* olefin **5**. Further, the Diels–Alder reaction of compound **5** was attempted by refluxing in toluene for about 60 h. However, starting material was recovered in this case. Changing the solvent from toluene to *o*-dichlorobenzene, refluxing for 36 h and

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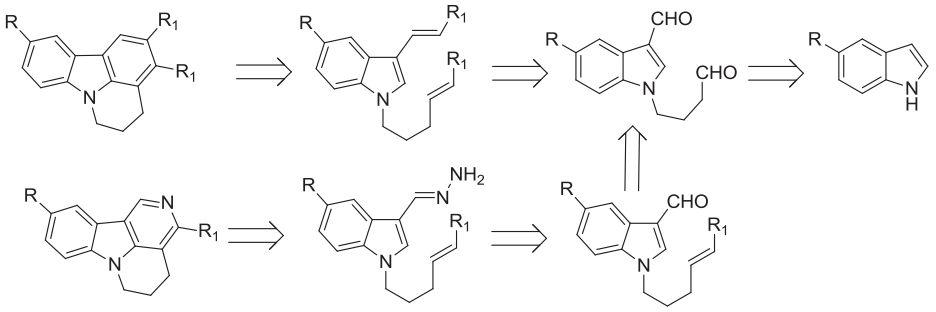
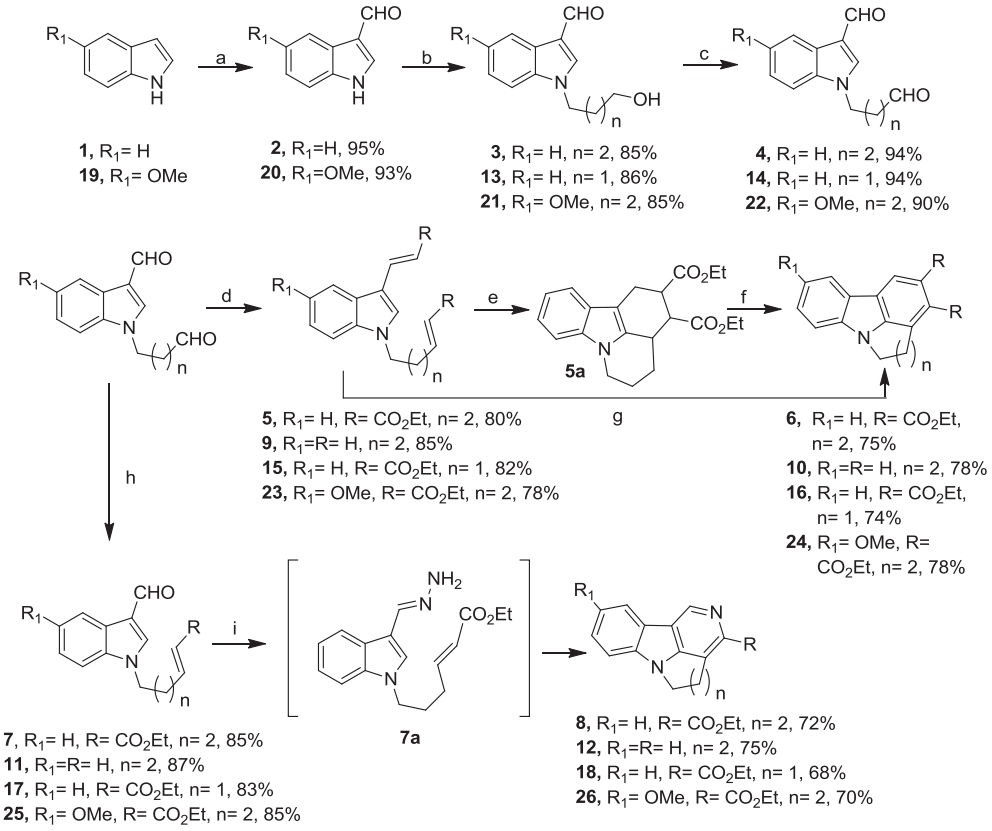


Scheme 1. Retrosynthetic analysis.

further purification led us to the desired cycloadduct **5a** in 78% yield. This compound was then characterised and was shown to be a single diastereomer from ^{1}H NMR spectral data. Nevertheless, the geometry of the isomer could not be fixed from the available data. This cycloadduct was further dehydrogenated using DDQ in *o*-dichlorobenzene to get the product[6] **6** as one of the targeted tetracyclic carbazoles in 75% yield. It was then thought to carry out the cycloaddition and dehydrogenation reaction in one pot with an aim to reduce the reaction time. Thus, compound **5** was refluxed in *o*-dichlorobenzene in presence of DDQ. As expected, tetracyclic carbazole **6** was produced after 36 h in 75% yield. From these experiments, it was revealed that a one pot reaction sequence having cycloaddition and dehydrogenation together was an efficient route considering the time and the yield of the reaction (Scheme 2).

isocanthine analogue. Thus, compound **4** was refluxed with 2 equiv of carbethoxymethylenetriphenyl phosphorane to furnish *trans* olefin **7** after 2 h. In subsequent step, use of imino diene system in the form of α,β-unsaturated hydrazone was envisioned in an aza-Diels–Alder reaction. Thus, compound **7** was refluxed for 60 h in toluene in presence of excess hydrazine hydrate. Instead of the expected hydrazone as the product, a new isocanthine derivative **8** was obtained in 72% yield. Formation of product **8** could be explained by initial in situ formation of hydrazone **7a**, followed by intramolecular aza-Diels–Alder reaction and dehydrogenation of the cycloadduct along with loss of ammonia. The efforts to isolate the intermediate hydrazone were unsuccessful because of the instability of the hydrazone.



Scheme 2. Reagents and conditions: a) DMF, $POCl_3$, rt, 5 h; b) KOH, DMSO, $ClCH_2(CH_2)_nCH_2OH$, rt, 5 h; c) IBX, EtOAc, 80 °C, 8 h; d) $PPh_3CHCOOEt$ (4 equiv), toluene, reflux, 8 h (for R=CO_2Et) or PPh_3CH_3I (4 equiv), ^{n}BuLi, THF, rt, 2 h (for R=H); e) *o*-dichlorobenzene, reflux, 36 h, 78%; f) DDQ, *o*-dichlorobenzene, reflux, 12 h, 75%; g) DDQ, *o*-dichlorobenzene, reflux, 36 h; h) $PPh_3CHCOOEt$ (2 equiv), toluene, reflux, 2 h or PPh_3CH_3I (2 equiv), ^{n}BuLi, THF, 30 min (R=H); i) NH_2–$NH_2\cdot H_2O$, toluene, reflux, 60 h.

Further, dialdehyde **4** formed in the above reaction sequence was used as a common starting material in order to obtain

Having the dialdehyde **4** in hand, unsubstituted tetracyclic carbazole and isocanthine derivatives were synthesised, following the

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same sequence of reactions. To accomplish this synthesis, Wittig reaction was performed with dialdehyde **4** using iodo(methyl)triphenylphosphorane (4 equiv) to get the olefin **9** after 2 h. It was then refluxed in *o*-dichlorobenzene–DDQ system, to furnish the known[13] target compound **10** as a tetracyclic carbazole derivative in a one pot sequence. The isocanthine analogue of this was also synthesised starting from the same dialdehyde **4** by treating it with iodo(methyl)triphenylphosphorane (2 equiv) for 30 min to give olefin **11**. This olefin, on treatment with hydrazine hydrate and further refluxing for 60 h gave the required isocanthine[10] derivative **12** in 75% yield in a similar one pot reaction sequence as shown earlier (Scheme 2).

As per our previous experience,[12] the size reduction of ring 'D' played an important role in increasing the biological activity of the compound. Thus, it was then planned to synthesise derivatives having a five-membered 'D' ring. For this purpose, indole-3-aldehyde **2** was initially *N*-alkylated with 3-chloro-propanol to give compound **13**, which on subsequent oxidation furnished the required intermediate dialdehyde **14**. Treatment of **14** with 4 equiv carbethoxymethylenetriphenyl phosphorane for 8 h afforded *trans* olefin **15**, whose treatment with DDQ in *o*-dichlorobenzene gave the targeted tetracyclic carbazole **16**. The isocanthine derivative with five-membered 'D' ring was obtained by initial reaction between dialdehyde **14** and carbethoxymethylenetriphenyl phosphorane (2 equiv) for 2 h giving *trans* olefin **17**. Further olefin **17** was refluxed with hydrazine hydrate in toluene to produce successfully a new unknown isocanthine derivative **18** in an aza-Diels–Alder reaction of the intermediate hydrazone (Scheme 2).

Review of the literature reports of canthine alkaloids indicated that, presence of methoxy substituent on the 'A' ring helps in increasing the biological activity. Taking into consideration the similarity of canthine framework with the isocanthine and tetracyclic carbazole moiety, we decided to synthesise analogues having methoxy substituent on 'A' ring. Starting with 5-methoxy indole **19**, the required dialdehyde intermediate **22** was obtained by sequentially following Vilsmeier–Haack formylation, N-alkylation with 4-chlorobutanol and IBX oxidation reactions. Similar to the set of reactions mentioned in above cases, compound **22** was treated with 4 equiv carbethoxymethylenetriphenyl phosphorane furnishing *trans* olefin **23** followed by refluxing with DDQ in *o*-dichlorobenzene to get the known[6] tetracyclic carbazole derivative **24**. The corresponding new isocanthine derivative **26** was obtained from dialdehyde **22**, by treating with 2 equiv carbethoxymethylenetriphenyl phosphorane to give *trans* olefin **25**, followed by refluxing with hydrazine hydrate in toluene.

2.1. Biological assay

After completing the synthesis of the targeted analogues, biological evaluation of some representative compounds was undertaken to evaluate cytotoxicity against HeLa cervical cancer cell lines, since the activity of these carbazoles was not studied earlier. The compounds chosen varied in the size of ring 'D' and substitution on 'A' ring. Thus the compounds **6**, **16** and **24** were dissolved in 2% DMSO (volume made up by PBS buffer) and diluted to micro molar (μM) concentration. The cell viability study was performed at an interval of 24 h, 48 h and 72 h. The IC_{50} values were obtained at the end of 72 h and are shown in Table 1. All the three compounds exhibited similar IC_{50} values ranging from 17 to 20 μM. The IC_{50} values indicate that, five membered D-ring is preferred over the six membered ring. Also, though the IC_{50} values are almost similar, a slightly lower IC_{50} value was shown by the compound **24**, compared to compound **6**, which may be owed to the presence of methoxy group on ring 'A'.

Table 1
IC_{50} values for carbazole analogues

Compound no.	IC_{50}/μM[a]
6	19.80±0.06
16	17.46±0.05
24	18.76±0.01

[a] IC_{50} values calculated from linear response from linear regression of the dose log response curves after 72 h exposure to the compound, determined by MTT assay on HeLa cell lines. Values are mean±SD of three experiments.

3. Conclusion

Thus, a new intramolecular Diels–Alder strategy using simple diene as well as its aza analogue in the form of hydrazone was successfully employed for the synthesis of four tetracyclic carbazoles and four isocanthines, respectively, in a clean and efficient manner. Some of the carbazoles were tested for activity against HeLa cervical cancer cell lines, which showed moderate activity with IC_{50} value of about 18 μM.

4. Experimental

4.1. General information

All reactions were carried out under an inert atmosphere with dry solvents, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (Kieselgel 60 F_{254}, Merck). Visualisation of the spots on TLC plates was achieved either by UV light or by staining the plates in 2,4-dinitrophenylhydrazine/anisaldehyde and charring on hot plate. All products were characterised by ^{1}H NMR and ^{13}C NMR, IR and HRMS/elemental analysis. ^{1}H NMR and ^{13}C NMR were recorded on Varian Mercury 300 MHz and 75 MHz instrument, respectively. Chemical shifts are expressed in parts per million values and ^{1}H NMR spectra are referenced to 0.00 ppm for Me_4Si (TMS) and ^{13}C NMR spectra are referenced to 77.00 ppm for $CDCl_3$. Peak multiplicities are designated by the following abbreviations: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; exch, D_2O exchangeable; *J*, coupling constant in Hertz. IR spectra were recorded on Bruker instrument as ATR. HRMS spectra were obtained on a Micromass Q-TOF apparatus. Melting points recorded are uncorrected. Column chromatography on silica gel (100–200 mesh) was performed with reagent grade ethyl acetate and hexane as an eluent.

4.2. Synthesis of formylated indoles 2 and 20

Prepared according to literature procedure.[14]

*4.2.1. 1H-Indole-3-carbaldehyde (**2**).* White solid (95%); mp[14] 195 °C.

*4.2.2. 5-Methoxy-1H-indole-3-carbaldehyde (**20**).* White solid (93%); mp[15] 180–182 °C; FTIR (ATR cm^{-1}) 3032, 2726, 1609, 1582, 1436, 1257, 1130, 1063; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.4 (1H, br s, –N*H*), 9.86 (1H, s, –C*H*O), 7.75 (1H, s, Ar*H*), 7.63 (1H, d, *J*=2.2 Hz, Ar*H*), 7.28 (1H, d, *J*=9.2 Hz, Ar*H*), 6.81 (1H, dd, *J*=2.2, 8.8 Hz, Ar*H*), 3.77 (3H, s, –OC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.7, 155.7, 136.8, 131.6, 124.7, 118.1, 113.4, 112.6, 102.5, 55.2.

4.3. General procedure for *N*-alkylindoles, 3, 13, 21

To a solution of DMSO (10 ml) taken in a round bottom flask was added KOH (2 equiv) and the solution was stirred at room temperature for 15 min. The indole derivative **2** or **20** (1 equiv) was

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then added and the mixture was further stirred for 1 h, after which 4-chlorobutan-1-ol or 3-chloropropan-1-ol (1.5 equiv) was added dropwise to the reaction mixture. The reaction was monitored by TLC to completion within 5 h. The reaction mixture was then quenched by adding water and was extracted with ethyl acetate. Evaporation of the solvent under reduced pressure followed by column chromatography gave the required *N*-alkylated compounds, **3**/**13**/**21**.

*4.3.1. 1-(4-Hydroxybutyl)-1H-indole-3-carbaldehyde (**3**).* White solid (85%); mp[12] 75–77 °C.

*4.3.2. 1-(3-Hydroxypropyl)-1H-indole-3-carbaldehyde (**13**).* Sticky solid[12] (86%).

*4.3.3. 1-(4-Hydroxybutyl)-5-methoxy-1H-indole-3-carbaldehyde (**21**).* Off white solid (84%); mp 89–91 °C; R_f (40% EA/Hexane) 0.35; FTIR (ATR cm^{-1}) 3299, 3094, 2929, 2856, 1638, 1620, 1529, 1435, 1194, 1043; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.86 (1H, s, −C*H*O), 7.76 (1H, d, *J*=2.4 Hz, Ar*H*), 7.65 (1H, s, Ar*H*), 7.25 (1H, d, *J*=9 Hz, Ar*H*), 6.94 (1H, dd, *J*=2.4, 8.6 Hz, Ar*H*), 4.16 (2H, t, *J*=7.1 Hz, −NCH_2), 3.87 (3H, s, −OCH_3), 3.65 (2H, t, *J*=6.2 Hz, −OCH_2), 2.28 (1H, br s, exch, −O*H*), 1.97 (2H, quint, *J*=7.6 Hz, −CH_2−), 1.56 (2H, quint, *J*=6.7 Hz, −CH_2−); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.5, 156.5, 138.5, 131.9, 126.0, 117.6, 114.2, 110.9, 103.3, 61.8, 55.7, 47.1, 29.5, 26.3; HRMS (ESI) (M+Na) 270.1104; calculated for $C_{14}H_{17}NO_3Na$ 270.1106.

4.4. General procedure for oxidation using IBX

To a solution of suitable hydroxyl compound **3**/**13**/**21** (1 equiv) in dry ethyl acetate (20 ml) was added *o*-iodoxybenzoic acid (1.5 equiv) under inert atmosphere. The contents were refluxed for 8 h and the reaction was followed by TLC. After completion of reaction, the reaction mixture was filtered through Celite bed on a sintered funnel and washed with ethyl acetate. Evaporation of the solvent under reduced pressure followed by column chromatography gave corresponding aldehydes **4**/**14**/**22**.

*4.4.1. 1-(4-Oxobutyl)-1H-indole-3-carbaldehyde (**4**).* Thick oil (93%); R_f (30% EA/Hexane) 0.53; FTIR (ATR cm^{-1}) 2936, 2813, 2725, 1718, 1650, 1576, 1467, 1165; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.95 (1H, s, −C*H*O), 9.75 (1H, s, −C*H*O), 8.27 (1H, dd, *J*=6.2, 2.4 Hz, Ar*H*), 7.67 (1H, s, Ar*H*), 7.28–7.41 (3H, m, Ar*H*), 4.22 (2H, t, *J*=7.1 Hz, −NCH_2), 2.49 (2H, t, *J*=7.1 Hz, −CH_2CHO), 2.18 (2H, quint, *J*=7.1 Hz, −CH_2−); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 200.4, 184.5, 138.1, 136.9, 125.3, 124.1, 122.9, 122.1, 118.1, 109.9, 45.9, 40.1, 22.1; HRMS (ESI) (M+Na) 238.0848; calculated for $C_{13}H_{13}NO_2Na$ 238.0844.

*4.4.2. 1-(3-Oxopropyl)-1H-indole-3-carbaldehyde (**14**).* Thick oil (94%); R_f (40% EA/Hexane) 0.55; FTIR (ATR cm^{-1}) 2946, 2820, 2729, 1720, 1656, 1577, 1468, 1169; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.85 (1H, s, −C*H*O), 9.68 (1H, s, −C*H*O), 8.23–8.25 (1H, m, Ar*H*), 7.72 (1H, s, Ar*H*), 7.23–7.30 (3H, m, Ar*H*), 4.41 (2H, t, *J*=6.6 Hz, −NCH_2), 3.00 (2H, t, *J*=6.6 Hz, −CH_2CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 198.6, 184.5, 139.4, 136.5, 125.1, 123.9, 122.8, 121.9, 117.9, 109.6, 42.7, 39.5; HRMS (ESI) (M+H) 202.0868; calculated for $C_{12}H_{12}NO_2$ 202.0868.

*4.4.3. 5-Methoxy-1-(4-oxobutyl)-1H-indole-3-carbaldehyde (**22**).* Thick oil (92%); R_f (40% EA/Hexane) 0.54; FTIR (ATR cm^{-1}) 2934, 2832, 1718, 1648, 1618, 1579, 1460, 1260, 1040; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.92 (1H, s, −C*H*O), 9.75 (1H, s, −C*H*O), 7.78 (1H, s, Ar*H*), 7.67 (1H, s, Ar*H*), 7.27 (1H, d, *J*=8.6 Hz, Ar*H*), 6.96 (1H, d, *J*=8.6 Hz, Ar*H*), 4.18 (2H, t, *J*=7.1 Hz, −NCH_2), 3.88 (3H, s, −OCH_3), 2.49 (2H, t, *J*=6.7 Hz, −CH_2CHO), 2.18 (2H, quint, *J*=7.1 Hz, −CH_2−); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 200.4, 184.4, 156.6, 138.1, 131.8, 126.1, 117.9, 114.5, 110.8, 103.3, 55.7, 46.1, 40.1, 22.1; HRMS (ESI) (M+Na) 268.0950; calculated for $C_{14}H_{15}NO_3Na$ 268.0950.

4.5. General procedure for synthesis of compounds 5, 15, 23

To a solution of suitable dialdehyde **4**/**14**/**22** (1 equiv) in dry toluene was added carbethoxymethylenetriphenyl phosphorane (4 equiv) and refluxed for 8 h under inert atmosphere. After the completion of reaction, toluene was concentrated under reduced pressure and the residue was extracted with ethyl acetate. Evaporation of the solvent under reduced pressure followed by column chromatography (0.5:9.5, EA/Hexane) gave corresponding compounds **5**/**15**/**23**.

*4.5.1. (E)-Ethyl 6-(3-((E)-3-ethoxy-3-oxoprop-1-en-1-yl)-1H-indol-1-yl)hex-2-enoate (**5**).* White solid (75%); mp 67–68 °C; R_f (30% EA/Hexane) 0.80; FTIR (ATR cm^{-1}) 2978, 2938, 1718, 1697, 1620, 1572, 1530, 1165, 1144; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.85–7.93 (2H, m, ArC*H*=CH−, Ar*H*), 7.21–7.34 (4H, m, Ar*H*), 6.84–6.94 (1H, m, −CH$_2$−C*H*=CH−), 6.41 (1H, d, *J*=15.8 Hz, −C*H*COOEt), 5.81 (1H, d, *J*=15.3 Hz, −C*H*COOEt), 4.26 (2H, q, *J*=7 Hz, −CH_2CH$_3$), 4.11–4.21 (4H, m, −NCH_2, −CH_2CH$_3$), 2.20 (2H, q, *J*=7.1 Hz, −CH_2−CH−), 2.02 (2H, quint, *J*=7.1 Hz, −CH_2−), 1.34 (3H, t, *J*=7 Hz, −CH$_2$CH_3), 1.28 (3H, t, *J*=7 Hz, −CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.1, 166.1, 146.6, 137.7, 137.1, 131.8, 126.1, 122.9, 122.5, 121.2, 120.7, 112.8, 112.2, 109.9, 60.2, 59.9, 45.7, 29.0, 28.0, 14.3, 14.1; HRMS (ESI) (M+Na) 378.1684; calculated for $C_{21}H_{25}NO_4Na$ 378.1681.

*4.5.2. (E)-Ethyl 5-(3-((E)-3-ethoxy-3-oxoprop-1-en-1-yl)-1H-indol-1-yl)pent-2-enoate (**15**).* White solid (82%); mp 109–111 °C; R_f (30% EA/Hexane) 0.84; FTIR (ATR cm^{-1}) 2974, 1713, 1697, 1618, 1470, 1152, 1046, 733; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.84–7.93 (2H, m, ArC*H*=CH−, Ar*H*), 7.22–7.37 (4H, m, Ar*H*), 6.84–6.94 (1H, m, −CH$_2$−C*H*=CH−), 6.41 (1H, d, *J*=16.4 Hz, −C*H*COOEt), 5.83 (1H, dt, *J*=15.8 and 0.9 Hz, −C*H*COOEt), 4.13–4.30 (6H, m, −NCH_2, −CH_2CH$_3$ ×2), 2.72 (2H, qd, *J*=7.1 and 0.9 Hz, −CH_2−CH=), 1.34 (3H, t, *J*=7.1 Hz, −CH$_2$CH_3), 1.26 (3H, t, *J*=7.1 Hz, −CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.1, 165.7, 143.2, 137.7, 137.0, 131.6, 126.1, 124.2, 123.0, 121.3, 120.7, 113.0, 112.4, 109.7, 60.4, 59.9, 45.2, 32.5, 14.4, 14.1; HRMS (ESI) (M+Na) 364.1526; calculated for $C_{20}H_{23}NO_4Na$ 364.1525.

*4.5.3. (E)-Ethyl 6-(3-((E)-3-ethoxy-3-oxoprop-1-en-1-yl)-5-methoxy-1H-indol-1-yl)hex-2-enoate (**23**).* White solid (78%); mp 85–87 °C; R_f (30% EA/Hexane) 0.78; FTIR (ATR cm^{-1}) 2922, 1714, 1692, 1605, 1519, 1456, 1320, 1156, 1034, 986; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.87 (1H, d, *J*=15.8 Hz, ArC*H*=CH−), 7.32 (2H, m, Ar*H*), 7.22 (1H, d, *J*=8.6 Hz, Ar*H*), 6.84–6.95 (2H, m, −CH$_2$−C*H*=CH−, Ar*H*), 6.32 (1H, d, *J*=15.7 Hz, −C*H*COOEt), 5.81 (1H, dt, *J*=15.7 and 1.4 Hz, −C*H*COOEt), 4.26 (2H, q, *J*=7.1 Hz, −CH_2CH$_3$), 4.15 (2H, q, *J*=7.1 Hz, −CH_2CH$_3$), 4.10 (2H, t, *J*=7.1 Hz, −NCH_2), 3.89 (3H, s, −OCH_3), 2.18 (2H, bq, *J*=6.7 Hz, −CH_2−CH−), 2.00 (2H, quint, *J*=7.1 Hz, −CH_2−), 1.34 (3H, t, *J*=7.1 Hz, −CH$_2$CH_3), 1.27 (3H, t, *J*=7.1 Hz, −CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.2, 166.2, 155.4, 146.6, 137.8, 132.2, 131.9, 126.7, 122.5, 112.9, 112.1, 111.8, 110.7, 102.6, 60.2, 60.0, 55.9, 45.9, 29.1, 28.1, 14.4, 14.1; HRMS (ESI) (M+Na) 408.1786; calculated for $C_{22}H_{27}NO_5Na$ 408.1787.

4.6. Synthesis of 1-(pent-4-en-1-yl)-3-vinyl-1*H*-indole (9)

To a solution of iodo(methyl)triphenylphosphorane (3.76 g, 9.3 mmol) in dry THF (50 ml) was added 1.6 M *n*-butyllithium (5.8 ml, 9.3 mmol) at 0 °C under nitrogen atmosphere. A yellow coloured anion was formed after which a solution of 1-(4-oxobutyl)-1*H*-indole-3-carbaldehyde (**4**) (0.5 g, 2.3 mmol) in dry THF (15 ml) was added dropwise to the above mixture. After the

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completion of reaction, the mixture was quenched by addition of saturated ammonium chloride solution and then extracted with ethyl acetate. Evaporation of the solvent under reduced pressure followed by column chromatography on neutral alumina (0.5:9.5, EA/Hexane) gave compound **9** as an unstable pale yellow oil (0.41 g, 85%). R_f (30% EA/Hexane) 0.81; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 (1H, d, J=7.6 Hz, Ar*H*), 7.33 (1H, d, J=8.1 Hz, Ar*H*), 7.24 (1H, m, Ar*H*), 7.14–7.21 (2H, m, Ar*H*), 6.88 (1H, dd, J=10.9, 17.6 Hz, ArC*H*=CH$_2$), 5.64–5.84 (2H, m, –CH$_2$–C*H*=CH$_2$, ArCH=C*H*H), 5.02–5.16 (3H, m, –CH$_2$–CH=C*H*$_2$, ArCH=CH*H*), 4.09 (2H, t, J=7.1 Hz, –NC*H*$_2$), 2.08 (2H, q, J=7.1 Hz, –C*H*$_2$–CH=), 1.93 (2H, quint, J=7.1 Hz, –C*H*$_2$–).

4.7. Synthesis of diethyl 2,3,3a,4,5,6-hexahydro-1*H*-pyrido [3,2,1-*jk*]carbazole-2,3-dicarboxylate (5a)

A solution of (*E*)-ethyl 6-(3-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)-1*H*-indol-1-yl)hex-2-enoate (**5**) (0.5 g, 1.4 mmol) in *o*-dichlorobenzene was refluxed under inert atmosphere for 36 h. After completion of reaction, water was added to the reaction mass and it was extracted with ethyl acetate. Evaporation of the solvent under reduced pressure followed by column chromatography (1:1, DCM/Hexane) gave compound **5a** as an off white solid (0.39 g, 78%). Mp 66–68 °C; R_f (30% EA/Hexane) 0.81; FTIR (ATR cm^{-1}) 2932, 1727 (br s), 1450, 1185, 1026, 742; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 (1H, d, J=7.2 Hz, ArH), 7.24–7.26 (1H, m, Ar*H*), 7.08–7.19 (2H, m, Ar*H*), 4.21–4.35 (3H, m, –C*H*$_2$CH$_3$, –C*H*COOEt), 4.06–4.19 (2H, m, –C*H*$_2$CH$_3$), 3.61–3.71 (2H, m, –NC*H*$_2$), 3.28–3.40 (2H, m, –C*H*$_2$CHCOOEt), 2.98–3.06 (1H, m, –CH$_2$C*H*COOEt), 2.58–2.66 (2H, m, –C*H*$_2$–), 2.16–2.25 (2H, m, –C*H*$_2$CH–), 1.34 (3H, t, J=7.1 Hz, –CH$_2$C*H*$_3$), 1.22 (3H, t, J=7.1 Hz, –CH$_2$C*H*$_3$), 1.11–1.17 (1H, m, –C*H*CHCOOEt); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.9, 172.5, 137.9, 135.4, 127.3, 120.8, 119.3, 117.9, 109.1, 104.9, 60.7, 60.6, 46.9, 42.5, 41.8, 32.0, 26.6, 23.2, 23.1, 14.1, 14.0; HRMS (ESI) (M+Na) 378.1673; calculated for $C_{21}H_{25}NO_4Na$ 378.1676.

4.8. General procedure for synthesis of tetracyclic carbazoles 6/10/16/24

To a stirred solution of **5**/**9**/**15**/**23** (1 equiv) in *o*-dichlorobenzene, was added DDQ (2.5 equiv) under inert atmosphere. The contents were refluxed for 36 h. After completion of reaction, water was added to the reaction mass and it was extracted with ethyl acetate. Evaporation of the solvent under reduced pressure followed by column chromatography (1:1, DCM/Hexane) gave compound **6**/**10**/**16**/**24**.

*4.8.1. Diethyl 5,6-dihydro-4H-pyrido[3,2,1-jk]carbazole-2,3-dicarboxylate (**6**).* Thick oil[6] (75%); FTIR (ATR cm^{-1}) 2924, 1711, 1599, 1578, 1475, 1261, 1140, 771; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.57 (1H, s, Ar*H*), 8.13 (1H, d, J=7.7 Hz, Ar*H*), 7.49–7.54 (1H, m, Ar*H*), 7.25–7.32 (1H, m, Ar*H*), 7.17–7.21 (1H, m, Ar*H*), 4.36–4.50 (4H, m, –C*H*$_2$CH$_3$ ×2), 4.20 (2H, t, J=5.7 Hz, –NC*H*$_2$), 3.06 (2H, t, J=6.2 Hz, ArC*H*$_2$), 2.31 (2H, quint, J=5.7 Hz, –C*H*$_2$–), 1.39–1.44 (6H, m, –CH$_2$C*H*$_3$ ×2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.3, 166.9, 140.8, 139.3, 130.4, 126.4, 122.5, 121.4, 121.3, 120.3, 119.9, 119.0, 118.6, 108.8, 61.4, 61.0, 40.7, 22.6, 21.8, 14.3, 14.2.

*4.8.2. 5,6-Dihydro-4H-pyrido[3,2,1-jk]carbazole (**10**).* Pale yellow solid (78%); mp[10] 86–88 °C; FTIR (ATR cm^{-1}) 2917, 1595, 1465, 1244, 1147, 743; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.27 (1H, d, J=7.2 Hz, Ar*H*), 7.86–7.92 (1H, m, Ar*H*), 7.4–7.5 (2H, m, Ar*H*), 7.29–7.38 (3H, m, Ar*H*), 4.10 (2H, t, J=6.6 Hz, –NC*H*$_2$), 2.97 (2H, t, J=6.6 Hz, ArC*H*$_2$–), 2.16 (2H, m, –C*H*$_2$–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.1, 136.9, 125.2, 123.9, 122.8, 122.5, 122.0, 120.8, 118.1, 117.6, 114.2, 109.8, 46.2, 28.9, 27.8.

*4.8.3. Diethyl 4,5-dihydropyrrolo[3,2,1-jk]carbazole-2,3-dicarboxylate (**16**).* Viscous oil (74%); R_f (30% EA/Hexane) 0.85; FTIR (ATR cm^{-1}) 2924, 1725, 1612, 1463, 1282, 1120, 744; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.59 (1H, s, Ar*H*), 8.12 (1H, d, J=7.7 Hz, Ar*H*), 7.49–7.54 (1H, m, Ar*H*), 7.25–7.32 (1H, m, Ar*H*), 7.17–7.21 (1H, m, Ar*H*), 4.26 (2H, q, J=7.1 Hz, –C*H*$_2$CH$_3$), 4.11–4.21 (4H, m, –NC*H*$_2$, –C*H*$_2$CH$_3$), 3.06 (2H, t, J=6.2 Hz, ArC*H*$_2$), 1.34 (3H, t, J=7.1 Hz, –CH$_2$C*H*$_3$), 1.28 (3H, t, J=7.1 Hz, –CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.3, 166.9, 140.8, 139.3, 130.4, 126.4, 122.5, 121.4, 121.3, 120.3, 119.9, 119.0, 118.6, 108.8, 61.4, 61.0, 40.7, 22.5, 14.3, 14.2; HRMS (ESI) (M+H) 338.1397; calculated for $C_{20}H_{20}NO_4$ 338.1392.

*4.8.4. Diethyl 10-methoxy-5,6-dihydro-4H-pyrido[3,2,1-jk]carbazole-2,3-dicarboxylate (**24**).* Thick brown oil[6] (78%); FTIR (ATR cm^{-1}) 2955, 2921, 1725, 1615, 1461, 1259, 1018; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.51 (1H, s, Ar*H*), 7.77 (1H, d, J=2.9 Hz, Ar*H*), 7.47 (1H, d, J=7.2 Hz, Ar*H*), 7.3–7.4 (1H, m, Ar*H*), 4.13–4.30 (6H, m, –NC*H*$_2$, –C*H*$_2$CH$_3$ ×2), 3.87 (3H, s, –OC*H*$_3$), 3.08 (2H, t, J=6.2 Hz, ArC*H*$_2$), 2.68–2.76 (2H, m, –C*H*$_2$–), 1.34 (3H, t, J=7.1 Hz, –CH$_2$C*H*$_3$), 1.26 (3H, t, J=7.2 Hz, –CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.2, 166.1, 146.6, 138.2, 137.1, 131.8, 126.0, 123.0, 122.5, 121.3, 120.7, 112.8, 112.3, 109.8, 60.2, 59.9, 55.8, 45.7, 29.1, 28.2, 14.3, 14.1.

4.9. General procedure for synthesis of compounds 7, 17, 25

To a solution of suitable dialdehyde **4**/**14**/**22** (1 equiv) in dry toluene was added carbethoxymethylenetriphenyl phosphorane (2 equiv) or and refluxed for 2 h under inert atmosphere. After the completion of reaction, toluene was concentrated under reduced pressure and the residue was extracted with ethyl acetate. Evaporation of the solvent under reduced pressure followed by column chromatography (2:8, EA/Hexane) gave corresponding compounds **7**/**17**/**25**.

*4.9.1. (E)-Ethyl 6-(3-formyl-1H-indol-1-yl)hex-2-enoate (**7**).* Pale yellow viscous oil (80%); R_f (30% EA/Hexane) 0.50; FTIR (ATR cm^{-1}) 2933, 1710, 1655, 1530, 1467, 1389, 1152, 1037, 744; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.97 (1H, s, –C*H*O), 8.27–8.30 (1H, m, Ar*H*), 7.66 (1H, s, Ar*H*), 7.25–7.33 (3H, m, Ar*H*), 6.82–6.92 (1H, m, –CH$_2$–C*H*=CH–), 5.80 (1H, d, J=15.8 Hz, –C*H*COOEt), 4.12–4.18 (4H, m, –NC*H*$_2$, –OC*H*$_2$CH$_3$), 2.20 (2H, q, J=7.1 Hz, –C*H*$_2$–CH–), 2.03 (2H, quint, J=6.7 Hz, –C*H*$_2$–), 1.25 (3H, t, J=7.2 Hz, –CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.4, 166.0, 146.2, 138.1, 136.9, 125.2, 123.9, 122.8, 122.5, 122.0, 118.0, 109.8, 60.2, 46.2, 28.9, 27.8, 14.1; HRMS (ESI) (M+Na) 308.1265; calculated for $C_{17}H_{19}NO_3Na$ 308.1263.

*4.9.2. (E)-Ethyl 5-(3-formyl-1H-indol-1-yl)pent-2-enoate (**17**).* Viscous oil (83%); R_f (30% EA/Hexane) 0.57; FTIR (ATR cm^{-1}) 2977, 2935, 1694, 1619, 1527, 1276, 1039, 740; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.98 (1H, s, –C*H*O), 8.31 (1H, m, Ar*H*), 7.70 (1H, d, J=7.6 Hz, Ar*H*), 7.26–7.38 (3H, m, Ar*H*), 6.85–7.06 (1H, m, –CH$_2$–C*H*=CH–), 5.94 (1H, d, J=15.7 Hz, –C*H*COOEt), 4.14–4.33 (4H, m, –NC*H*$_2$, –C*H*$_2$CH$_3$), 2.50 (2H, q, J=7.1 Hz, –C*H*$_2$–CH–), 1.25 (3H, t, J=6.7 Hz, –CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.4, 172.3, 146.2, 138.1, 137.1, 125.4, 124.0, 122.9, 122.5, 122.1, 118.2, 109.9, 60.7, 46.1, 30.7, 14.1; HRMS (ESI) (M+Na) 294.1109; calculated for $C_{16}H_{17}NO_3Na$ 294.1106.

*4.9.3. (E)-Ethyl 6-(3-formyl-5-methoxy-1H-indol-1-yl)hex-2-enoate (**25**).* Pale yellow oil (80%); R_f (30% EA/Hexane) 0.58; FTIR (ATR cm^{-1}) 2948, 2786, 1706, 1650, 1514, 1265, 1097; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.45 (1H, s, –C*H*O), 7.81 (1H, s, Ar*H*), 7.22 (1H, d, J=3.1 Hz,

ArH), 7.00 (1H, d, J=8.1 Hz, ArH), 6.83–6.93 (1H, m, $-CH_2-CH=$ CH−), 6.72, (1H, d, J=7.7 Hz, ArH), 5.81 (1H, d, J=15.7 Hz, −CHCOOEt), 4.1–4.2 (4H, m, $-NCH_2$, $-CH_2CH_3$), 3.99 (3H, s, $-OCH_3$), 2.20 (2H, q, J=6.7 Hz, $-CH_2-CH-$), 2.05 (2H, quint, J=6.6 Hz, $-CH_2-$), 1.28 (3H, t, J=6.7 Hz, $-CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.9, 166.2, 154.7, 146.3, 137.9, 130.8, 123.8, 122.6, 118.3, 116.9, 103.4, 102.4, 60.3, 55.3, 46.5, 29.0, 28.0, 14.2; HRMS (ESI) (M+Na) 338.1367; calculated for $C_{18}H_{21}NO_4Na$ 338.1368.

4.10. Synthesis of 1-(pent-4-en-1-yl)-1*H*-indole-3-carbaldehyde (11)

To a solution of iodo(methyl)triphenylphosphorane (0.75 g, 1.8 mmol) in dry THF (20 ml) was added 1.6 M *n*-butyllithium (1.0 ml, 1.8 mmol) at 0 °C under nitrogen atmosphere. A yellow coloured anion was formed after which a solution of 1-(4-oxobutyl)-1*H*-indole-3-carbaldehyde (**4**) (0.2 g, 0.9 mmol) in dry THF (5 ml) was added dropwise to the above mixture. After the completion of reaction, the mixture was quenched by addition of saturated ammonium chloride solution and then extracted with ethyl acetate. Evaporation of the solvent under reduced pressure followed by column chromatography on neutral alumina (2:8, EA/Hexane) gave compound 11 as an unstable pale yellow oil (0.17 g, 87%); R_f (30% EA/Hexane) 0.65; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.0 (1H, s, −CHO), 8.29–8.32 (1H, m, ArH), 7.71 (1H, s, ArH), 7.28–7.40 (3H, m, ArH), 5.73–5.86 (1H, m, $-CH_2-CH=CH_2$), 5.03–5.10 (2H, m, $-CH_2-CH=CH_2$), 4.19 (2H, t, J=7.1 Hz, $-NCH_2$), 2.11 (2H, q, J=7.1 Hz, $-CH_2-CH=$), 2.01 (2H, quint, J=7.1 Hz, $-CH_2-$).

4.11. General procedure for synthesis of isocanthine analogues 8/12/18/26

To a solution of **7**/**11**/**17**/**25** (1 equiv) in toluene was added hydrazine hydrate in excess (1 ml). The reaction mixture was then refluxed for 50–60 h. Toluene was then removed under reduced pressure and the residue was extracted with ethyl acetate. Evaporation of the solvent under reduced pressure followed by column chromatography (1.5:8.5, EA/Hexane) gave compounds **8**/**12**/**18**/**26**.

*4.11.1. Ethyl 5,6-dihydro-4H-indolo[3,2,1-ij][1,6]naphthyridine-3-carboxylate (**8**).* Thick oil (62%); R_f (35% EA/Hexane) 0.55; FTIR (ATR cm^{-1}) 2925, 1713, 1654, 1531, 1366, 1182, 1040; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.97 (1H, s, ArH), 8.30 (1H, d, J=7.7 Hz, ArH), 7.22–7.36 (3H, m, ArH), 4.22–4.29 (4H, m, $-NCH_2$, $-CH_2CH_3$), 2.14–2.27 (4H, m, $ArCH_2$, $-CH_2-$), 1.34 (3H, t, J=7.1 Hz, $-CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.1, 137.5, 137.0, 131.7, 126.2, 123.3, 121.6, 120.9, 118.5, 113.5, 112.8, 109.8, 60.1, 44.6, 29.5, 25.7, 14.4; HRMS (ESI) (M+H) 281.1290; calculated for $C_{17}H_{17}N_2O_2$ 281.1290.

*4.11.2. 5,6-Dihydro-4H-indolo[3,2,1-ij][1,6]naphthyridine (**12**).* Dark yellow solid (75%); mp[14] 275 °C (dec); FTIR (ATR cm^{-1}) 2920, 1620, 1574, 1478, 1242, 1167, 748; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.09 (1H, s, ArH), 8.22 (1H, s, ArH), 7.90 (1H, d, J=7.4 Hz, ArH), 7.22–7.36 (3H, m, ArH), 4.36 (2H, t, J=6.7 Hz, $-NCH_2$), 3.63 (2H, t, J=5.7 Hz, $ArCH_2$), 2.09 (2H, quint, J=6.2 Hz, $-CH_2-$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.8, 137.5, 136.0, 133.5, 131.4, 125.4, 123.6, 122.3, 120.5, 110.6, 107.9, 46.8, 29.5, 26.3.

*4.11.3. Ethyl 4,5-dihydrobenzo[b]pyrido[3,4,5-gh]pyrrolizine-3-carboxylate (**18**).* Dark brown thick oil (68%); R_f (30% EA/Hexane) 0.61; FTIR (ATR cm^{-1}) 2931, 1694, 1616, 1466, 1093, 738; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.18 (1H, s, ArH), 8.29 (1H, d, J=8.6 Hz, ArH), 7.25–7.42 (3H, m, ArH), 4.25 (2H, t, J=7.2 Hz, $-NCH_2$), 4.12 (2H, q, J=7.2 Hz, $-CH_2CH_3$), 3.06 (2H, t, J=6.2 Hz, $ArCH_2$), 1.23 (3H, t, J=7.2 Hz, $-CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.9, 137.1, 136.5, 131.1, 126.3, 123.5, 121.8, 121.0, 116.7, 114.1, 113.4, 109.2, 60.1, 42.1, 18.9, 14.3; HRMS (ESI) (M+H) 267.1133; calculated for $C_{16}H_{15}N_2O_2$ 267.1133.

*4.11.4. Ethyl 10-methoxy-5,6-dihydro-4H-indolo[3,2,1-ij][1,6]naphthyridine-3-carboxylate (**26**).* Viscous oil (70%); R_f (25% EA/Hexane) 0.61; FTIR (ATR cm^{-1}) 2976, 2927, 1718, 1619, 1469, 1366, 1038, 797; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.86 (1H, s, ArH), 7.77 (1H, d, J=2.4 Hz, ArH), 7.25 (1H, d, J=9 Hz, ArH), 6.94 (1H, dd, J=2.4, 8.6 Hz, ArH), 4.39 (2H, q, J=7.1 Hz, $-CH_2CH_3$), 4.16 (2H, t, J=7.1 Hz, $-NCH_2$), 3.87 (3H, s, $-OCH_3$), 3.65 (2H, t, J=6.2 Hz, $ArCH_2$), 1.97 (2H, m, $-CH_2-$), 1.23 (3H, t, J=7.1 Hz, $-CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.3, 137.9, 137.2, 132.1, 126.0, 122.7, 121.1, 120.6, 112.4, 111.9, 110.0, 108.3, 61.9, 60.1, 46.5, 29.7, 26.5, 14.5; HRMS (ESI) (M+H) 311.1396; calculated for $C_{18}H_{19}N_2O_3$ 311.1395.

4.12. Cytotoxicity test

The cytotoxicity of the compounds was measured at 24, 48 and 72 h intervals in triplicate using a standard MTT assay against human cervical cell line (HeLa). The average cytotoxicity data and the associated standard deviation (SD) obtained were then used to calculate cell viability.[16]

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